REMARKS

These remarks are in response to the Office Action mailed August 14, 2001.

Specification

- 3a. The title has been amended to comport with the claims.
- 3b. Applicant's attorney had not provided a reference list due to computer problems.

 An alphabetical reference list is provided herewith. Examiner is respectfully requested to append this list to the application. No new matter is being added.
- 3c. This was amended by addition of the reference list.
- 3d. On page 3, lines 14 and 24 refer to tumor necrosis factor-alpha (TNF α).
 - On page 25, line 9; page 27, line 19, the ? should read μ .
- On page 31, line 24, the glasses should be β . The symbols were improperly represented because the application was printed using another computer that did not have the same symbol codes. Applicant's attorney wishes to apologize.
- 3f. This table is part of a definition of amino acid, and does not relate to the description. It may be removed if desired.
- 4. Sequence listing in computer readable form and hard copy are enclosed herewith.

Claim Rejections - 35 USC §112, second paragraph

- 5a. These claims have been amended.
- 5b. These claims have been amended to include members of a group of TNF superfamily of proteins.
- 5c. ... "[S]aid ligand strand" in line 19 has been amended to "said first ligand strand."
- 5d. Claim 7 has been amended been amended to indicate that the hybrid strands are bound to each other in parallel fashion in the stalk region.

5e. Examiner has rejected claim 7 as being vague and indefinite in the recitation of the term "carbohydrate recognition domains (CRD)" for the reason that it is "unclear what sequences are encompassed in the carbohydrate recognition domains."

The CRD sequence has been removed from each SPD molecule by substitution with a TNFSF sequence, and so no longer exists in the invention. The construct consists of an SPD sequence-CRD fused in tandem with a TNFSF sequence. Therefore, a listing for CRD has not been provided.

Applicant respectfully requests that this rejection be withdrawn.

- 5f. The amendment of claim 7 now states that the first trimer strand, TNFSF, is joined in tandem with the second trimer strand, (SPD minus CRD). Applicant made the change suggested by Examiner, but also made additional changes in order to help clarify the claim elements.
- 5g. Claim 8 has been amended to define "functional equivalents" as "immunostimulatory functional equivalents".
- 5h. It is intended by the claim language to include <u>any</u> modifications to the fused protein, including any modifications to TNFSF, because a modification might make a TNFSF moiety fall out of the recognized nomenclature, while retaining functions of, both, TNF and this fused protein.

Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections - 35 USC s 112, first paragraph

6a,b. Examiner rejected claim 8 as not being commensurate in scope with the written description. In other words, the written description does not provide support for the claim as written. Applicant respectfully disagrees.

On page 36 of the application, Applicant clearly states his reasons for wording claim 8 as he has. In the paragraph immediately below Table II, lines 2 - 7, Applicant

relates the properties of all known collectins in the superfamily, the "tight" similarities between the known CRD structures and extracellular domains of TNFSF members, and the likelihood that any collectin CRD could be replaced with the extracellular domain of any TNFSF member in a structurally compatible manner. This conclusion is based on a sound intellectual premise and deduction. Certainly Applicant has described what he "has conceived". The other TNFSF member sequences are defined in the literature and are available to anyone skilled in the art. The properties required for the functional analogy are stated on page 36. Certainly, given the fact that all TNFSF members have the required properties, and the availability of the sequences in the literature and repositories, one skilled in the art could combine the materials and methods to come up with the claimed invention without undue experimentation.

Applicant based his conclusion on the following premises. It is presumed that TNFSF members stimulate the immune response, and that the collectins, all having very similar structures and properties will fuse with TNFSF members because of the latters' similar structures for the purpose of substituting for CRD moieties. It is a known fact that all known TNFSF members stimulate the immune response. It is also known that all TNFSF and CRD have compatible binding capacities with collectin moieties. Therefore, it follows that all TNFSF members would, with substantial certainty, fuse with collectin moieties to produce a fusion protein having the capacity to stimulate the immune response.

Applicant respectfully requests that this rejection be withdrawn.

7. Applicant appreciates Examiner's assessment of the prior art, and that the claims do not read on the prior art.

CONCLUSION

In summary, for the reasons set forth herein, Applicant maintains that claims 7 and 8, as now amended, clearly and patentably define the invention. Therefore,

Applicant respectfully requests that the Examiner reconsider the various grounds set forth in the Office Action, and allow all claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' representative can be reached at (760) 788-7401.

Respectfully submitted,

Date: January 14, 2002

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REFERENCES

Banchereau, J., and R.M. Steinman. 1998. Dendritic cells and the control of immunity. *Nature* 392:245-252.

Bazzoni, F., and B. Beutler. 1996. The tumor necrosis factor ligand and receptor families. *New England Journal of Medicine* 334:1717-1725.

Brown-Augsburger, P., K. Hartshorn, D. Chang, K. Rust, C. Fliszar, H.G. Welgus, and E.C. Crouch. 1996. Site-directed mutagenesis of Cys-15 and Cys-20 of pulmonary surfactant protein D. Expression of a trimeric protein with altered anti-viral properties. *Journal of Biological Chemistry* 271:13724-13730.

Chen, C.A., and H. Okayama. 1988. Calcium phosphate-mediated gene transfer: a highly efficient transfection system for stably transforming cells with plasmid DNA. *Biotechniques* 6:632-638.

Crouch, E., A. Persson, D. Chang, and J. Heuser. 1994. Molecular structure of pulmonary surfactant protein D (SP-D). *Journal of Biological Chemistry* 269:17311-17319.

Crouch, E., D. Chang, K. Rust, A. Persson, and J. Heuser. 1994. Recombinant pulmonary surfactant protein D. Post-translational modification and molecular assembly. Journal of Biological Chemistry 269:15808-15813.

Crouch, E.C. 1998. Structure, biologic properties, and expression of surfactant protein D (SP-D). *Biochimica et Biophysica Acta* 1408:278-289.

Dalum, I., D.M. Butler, M.R. Jensen, P. Hindersson, L. Steinaa, A.M. Waterston, S.N. Grell, M. Feldmann, H.I. Elsner, and S. Mouritsen. 1999. Therapeutic antibodies elicited by immunization against TNF-alpha. *Nature Biotechnology* 17:666-669.

Dhodapkar, M.V., R.M. Steinman, M. Sapp, H. Desai, C. Fossella, J. Krasovsky, S.M. Donahoe, P.R. Dunbar, V. Cerundolo, D.F. Nixon, and N. Bhardwaj. 1999. Rapid generation of broad T-cell immunity in humans after a single injection of mature dendritic cells. *Journal of Clinical Investigation* 104:173-180.

Dong, Q., and J.R. Wright. 1998. Degradation of surfactant protein D by alveolar macrophages. *American Journal of Physiology* 274:L97-105.

Fanslow, W.C., S. Srinivasan, R. Paxton, M.G. Gibson, M.K. Spriggs, and R.J. Armitage. 1994. Structural characteristics of CD40 ligand that determine biological function. *Seminars in Immunology* 6:267-278.

Grell, M., E. Douni, H. Wajant, M. Löhden, M. Clauss, B. Maxeiner, S. Georgopoulos, W. Lesslauer, G. Kollias, K. Pfizenmaier, and et al. 1995. The transmembrane form of tumor necrosis factor is the prime activating ligand of the 80 kDa tumor necrosis factor receptor. *Cell* 83:793-802.

Gruss, H.J., and S.K. Dower. 1995. Tumor necrosis factor ligand superfamily: involvement in the pathology of malignant lymphomas. *Blood* 85:3378-3404.

Gurunathan, S., K.R. Irvine, C.Y. Wu, J.I. Cohen, E. Thomas, C. Prussin, N.P. Restifo, and R.A. Seder. 1998. CD40 ligand/trimer DNA enhances both humoral and cellular immune responses and induces protective immunity to infectious and tumor challenge. *Journal of Immunology* 161:4563-4571.

Higgins, L.M., S.A. McDonald, N. Whittle, N. Crockett, J.G. Shields, and T.T. MacDonald. 1999. Regulation of T cell activation in vitro and in vivo by targeting the

OX40-OX40 ligand interaction: amelioration of ongoing inflammatory bowel disease with an OX40-IgG fusion protein, but not with an OX40 ligand-IgG fusion protein.

Journal of Immunology 162:486-493.

Hollenbaugh, D., N.J. Chalupny, and A. Aruffo. 1992. Recombinant globulins: novel research tools and possible pharmaceuticals. *Current Opinion in Immunology* 4:216-219.

Hoppe, H.J., and K.B. Reid. 1994. Collectins--soluble proteins containing collagenous regions and lectin domains--and their roles in innate immunity. *Protein Science* 3:1143-1158.

Hoppe, H.J., P.N. Barlow, and K.B. Reid. 1994. A parallel three stranded alphahelical bundle at the nucleation site of collagen triple-helix formation. *Febs Letters* 344:191-195.

Kato, K., E. Santana-Sahagun, L. Rassenti, M. Weisman, N. Tamura, S. Kobayashi, H. Hashimoto, and T. Kipps. 1999. The soluble CD40 ligand sCD154 in systemic lupus erythematosus. *J. Clin. Invest.* 104:947-955.

Kehry, M., B. Castle, and P. Hodgkin. 1992. B-cell activation mediated by interactions with membranes from helper T cells. *In* Mechanisms of Lymphocyte Activation and Immune Regulation IV: Cellular Communications, vol. 323. S. Gupta and T. Waldmann, editors. Plenum Press, New York. 139.

Kehry, M.R., and B.E. Castle. 1994. Regulation of CD40 ligand expression and use of recombinant CD40 ligand for studying B cell growth and differentiation. *Seminars in Immunology* 6:287-294.

Kikuchi, T., and R.G. Crystal. 1999. Anti-tumor immunity induced by in vivo adenovirus vector-mediated expression of CD40 ligand in tumor cells. *Human Gene Therapy* 10:1375-1387.

Kingston, R., R. Kaufman, C. Bebbington, and M. Rolfe. 1999. Amplification using CHO expression vectors. *In* Current Protocols in Molecular Biology, vol. 3. F. Ausubel, R. Brent, R. Kingston, D. Moore, J. Seidman, J. Smithe and K. Struhl, editors. 4 vols. John Wiley & Sons, Inc., New York. 16.14.11-16.14.13.

Klaus, G.G., M. Holman, C. Johnson-Léger, J.R. Christenson, and M.R. Kehry. 1999. Interaction of B cells with activated T cells reduces the threshold for CD40-mediated B cell activation. *International Immunology* 11:71-79.

Kornbluth, R.S., K. Kee, and D.D. Richman. 1998. CD40 ligand (CD154) stimulation of macrophages to produce HIV-1-suppressive beta-chemokines. *Proceedings* of the National Academy of Sciences of the United States of America 95:5205-5210.

Kuroki, Y., and D.R. Voelker. 1994. Pulmonary surfactant proteins. *Journal of Biological Chemistry* 269:25943-25946.

Kwon, B., B.S. Youn, and B.S. Kwon. 1999. Functions of newly identified members of the tumor necrosis factor receptor/ligand superfamilies in lymphocytes. *Current Opinion in Immunology* 11:340-345.

Lane, P., T. Brocker, S. Hubele, E. Padovan, A. Lanzavecchia, and F. McConnell. 1993. Soluble CD40 ligand can replace the normal T cell-derived CD40 ligand signal to B cells in T cell-dependent activation. *Journal of Experimental Medicine* 177:1209-1213.

Lu, J., H. Wiedemann, U. Holmskov, S. Thiel, R. Timpl, and K.B. Reid. 1993. Structural similarity between lung surfactant protein D and conglutinin. Two distinct, C-

type lectins containing collagen-like sequences. *European Journal of Biochemistry* 215:793-799.

Mach, F., U. Schönbeck, J.Y. Bonnefoy, J.S. Pober, and P. Libby. 1997. Activation of monocyte/macrophage functions related to acute atheroma complication by ligation of CD40: induction of collagenase, stromelysin, and tissue factor. *Circulation* 96:396-399.

Malik, N., B.W. Greenfield, A.F. Wahl, and P.A. Kiener. 1996. Activation of human monocytes through CD40 induces matrix metalloproteinases. *Journal of Immunology* 156:3952-3960.

Mariani, S.M., B. Matiba, T. Sparna, and P.H. Krammer. 1996. Expression of biologically active mouse and human CD95/APO-1/Fas ligand in the baculovirus system. Journal of Immunological Methods 193:63-70.

Mendoza, R.B., M.J. Cantwell, and T.J. Kipps. 1997. Immunostimulatory effects of a plasmid expressing CD40 ligand (CD154) on gene immunization. *Journal of Immunology* 159:5777-5781.

Morris, A.E., R.L. Remmele, Jr., R. Klinke, B.M. Macduff, W.C. Fanslow, and R.J. Armitage. 1999. Incorporation of an isoleucine zipper motif enhances the biological activity of soluble CD40L (CD154). *Journal of Biological Chemistry* 274:418-423.

Motwani, M., R.A. White, N. Guo, L.L. Dowler, A.I. Tauber, and K.N. Sastry. 1995. Mouse surfactant protein-D. cDNA cloning, characterization, and gene localization to chromosome 14. *Journal of Immunology* 155:5671-5677.

Oyaizu, N., N. Kayagaki, H. Yagita, S. Pahwa, and Y. Ikawa. 1997. Requirement of cell-cell contact in the induction of Jurkat T cell apoptosis: the membrane-anchored

but not soluble form of FasL can trigger anti-CD3-induced apoptosis in Jurkat T cells. Biochemical and Biophysical Research Communications 238:670-675.

Pietravalle, F., S. Lecoanet-Henchoz, J.P. Aubry, G. Elson, J.Y. Bonnefoy, and J.F. Gauchat. 1996. Cleavage of membrane-bound CD40 ligand is not required for inducing B cell proliferation and differentiation. *European Journal of Immunology* 26:725-728.

Pullen, S.S., M.E. Labadia, R.H. Ingraham, S.M. McWhirter, D.S. Everdeen, T. Alber, J.J. Crute, and M.R. Kehry. 1999. High-affinity interactions of tumor necrosis factor receptor-associated factors (TRAFs) and CD40 require TRAF trimerization and CD40 multimerization. *Biochemistry* 38:10168-10177.

Ruiz, S., A.H. Henschen-Edman, H. Nagase, and A.J. Tenner. 1999. Digestion of C1q collagen-like domain with MMPs-1,-2,-3, and -9 further defines the sequence involved in the stimulation of neutrophil superoxide production. *Journal of Leukocyte Biology* 66:416-422.

Schneider, P., N. Holler, J.L. Bodmer, M. Hahne, K. Frei, A. Fontana, and J. Tschopp. 1998. Conversion of membrane-bound Fas(CD95) ligand to its soluble form is associated with downregulation of its proapoptotic activity and loss of liver toxicity. *Journal of Experimental Medicine* 187:1205-1213.

Schuchmann, M., S. Hess, P. Bufler, C. Brakebusch, D. Wallach, A. Porter, G. Riethmüller, and H. Engelmann. 1995. Functional discrepancies between tumor necrosis factor and lymphotoxin alpha explained by trimer stability and distinct receptor interactions. *European Journal of Immunology* 25:2183-2189.

Schultze, J.L., S. Michalak, M.J. Seamon, G. Dranoff, K. Jung, J. Daley, J.C. Delgado, J.G. Gribben, and L.M. Nadler. 1997. CD40-activated human B cells: an

alternative source of highly efficient antigen presenting cells to generate autologous antigen-specific T cells for adoptive immunotherapy. *Journal of Clinical Investigation* 100:2757-2765.

Seyama, K., S. Nonoyama, I. Gangsaas, D. Hollenbaugh, H.F. Pabst, A. Aruffo, and H.D. Ochs. 1998. Mutations of the CD40 ligand gene and its effect on CD40 ligand expression in patients with X-linked hyper IgM syndrome. *Blood* 92:2421-2434.

Shapiro, L., and P.E. Scherer. 1998. The crystal structure of a complement-1q family protein suggests an evolutionary link to tumor necrosis factor. *Current Biology* 8:335-338.

Shimizu, H., J.H. Fisher, P. Papst, B. Benson, K. Lau, R.J. Mason, and D.R. Voelker. 1992. Primary structure of rat pulmonary surfactant protein D. cDNA and deduced amino acid sequence. *Journal of Biological Chemistry* 267:1853-1857.

Smith, C.A., T. Farrah, and R.G. Goodwin. 1994. The TNF receptor superfamily of ceitular and viral proteins: activation, costimulation, and death. *Cell* 76:959-962.

Suda, T., H. Hashimoto, M. Tanaka, T. Ochi, and S. Nagata. 1997. Membrane Fas ligand kills human peripheral blood T lymphocytes, and soluble Fas ligand blocks the killing. *Journal of Experimental Medicine* 186:2045-2050.

Tesselaar, K., L.A. Gravestein, G.M. van Schijndel, J. Borst, and R.A. van Lier. 1997. Characterization of murine CD70, the ligand of the TNF receptor family member CD27. *Journal of Immunology* 159:4959-4965.

Urlaub, G., E. Käs, A.M. Carothers, and L.A. Chasin. 1983. Deletion of the diploid dihydrofolate reductase locus from cultured mammalian cells. *Cell* 33:405-412.

Venolia, L., G. Urlaub, and L.A. Chasin. 1987. Polyadenylation of Chinese hamster dihydrofolate reductase genomic genes and minigenes after gene transfer. Somatic Cell and Molecular Genetics 13:491-504.

Wong, B.R., R. Josien, S.Y. Lee, B. Sauter, H.L. Li, R.M. Steinman, and Y. Choi. 1997. TRANCE (tumor necrosis factor [TNF]-related activation-induced cytokine), a new TNF family member predominantly expressed in T cells, is a dendritic cell-specific survival factor. *Journal of Experimental Medicine* 186:2075-2080.

Wong, C.P., C.Y. Okada, and R. Levy. 1999. TCR vaccines against T cell lymphoma: QS-21 and IL-12 adjuvants induce a protective CD8+ T cell response. Journal of Immunology 162:2251-2258.

Zipp, F., R. Martin, R. Lichtenfels, W. Roth, J. Dichgans, P.H. Krammer, and M. Weller. 1997. Human autoreactive and foreign antigen-specific T cells resist apoptosis induced by soluble recombinant CD95 ligand. *Journal of Immunology* 159:2108-2115.